REMARKS

Claims 12-17 and 33 are currently pending in the application. Claim 12 is amended by the present communication. The subject amendment merely corrects an apparent typographical error and is supported by the specification at, for example, p. 12, l. 4 and the claims as originally filed. No new matter is introduced by the present amendment. Upon entry of the present amendment, claims 12-17 and 33 and will remain pending and under consideration.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12-17 and 33 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. Applicants traverse the rejection as applied to the pending claims, for the reasons of record and those that follow.

The Office Action alleges, in pertinent part, that the specification is not enabling because at the time of the invention the state of the art as it pertains to the transplantation of neural progenitor cells for therapy were not routinely achievable by those skilled in the art, citing several references in efforts to support this position.

Applicants submit that the claims are enabled because the specification provides appropriate guidance, working examples, and prediction of function based on the observed properties of immortalized CNS progenitor cells such that one of skill in the art could practice the invention as claimed. Moreover, a post-filing reference submitted herewith confirms the operability of the present methods.

The present specification provides general teachings of how to make the cells of the present invention disclosed (*e.g.*, Example 1), as well as specific examples for the production of differentiated cells (*e.g.*, Example 2). Moreover, standardized methods for the treatment of subjects, including routes and frequency of administration, are disclosed (see, *e.g.*, p. 19, l. 18 bridging to p., 20, l. 27). And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., Johns Hopkins University v. Cellpro,

Inc., 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), where the court stated that "experimentation does not constitute undue experimentation" where "it is merely routine.").

In addition, Applicants previously provided a number of references as evidence that, at the time the application was filed, immortalized cells have the developmental plasticity to respond to local microenvironmental signals and the adult brain retains the capacity to direct differentiation of these cells. For example, Snyder et al. (1992) demonstrates that immortalized cell lines transformed by *v-myc* are capable of engraftment and differentiation into neurons or glia in a manner appropriate to their site of engraftment, where such cells could be identified in animals up to 22 months postengraftment (see Abstract and Results). Gao and Hatten (1994) demonstrate that immortalized cells (in contrast to primary external germ layer (EGL) cells) give rise to multiple types of cells after implantation. The authors further provide their finding are consistent with Renfranz et al. (1991), in that immortalized progenitor cells differentiated into a variety of cerebellar cell classes after early implantation (p. 1067, col. 2, second paragraph). Further, Gao and Hatten (1994) were able to show that their results were consistent with Snyder et al. (1992), where it was shown that immortalized cerebellar cells can participate in the formation of the cerebellum. Moreover, Shihabuddin et al. (1995) demonstrate that immortalized cells showed consistent morphology within their transplantation site, and that, again, immortalized cells have the developmental plasticity to respond to local microenvironmental signals and that the adult brain retains the capacity to direct differentiation of neuronal precursor cells in a direction that is consistent with that of endogenous neurons (e.g., Abstract and Results).

The Examiner asserts however, that studies in which progenitor cells are implanted into a normal brain are not necessarily predictive of a therapeutic response in a diseased brain. In response, Applicants provide a post-filing reference that confirms the operability of the claimed methods. Applicants respectfully remind the Examiner that it is well-established that the Applicant is not precluded from "providing a declaration after the filing date which demonstrates that the claimed invention works." M.P.E.P. § 2164.05. Indeed, later dated publications may properly be submitted as evidence that a disclosure was in fact enabled when it was filed. *See In*

re Branna, 51 F.3d 1560, 1567, 34 USPQ2d 1436 n.19 (Fed. Cir. 1995). As stated by the Board of Patent Appeals and Interferences, "post-filing evidence can be relied on for certain purposes," one of which is "as evidence that the disclosed device would have been operative." *Ex parte Lal*, Appeal 2007-2517 (Bd. Pat.App. & Interf. 2007); *see also Ex parte Olson*, Appeal 2007-4153 (Bd. Pat.App. & Interf. 2008). This has been supported by the Federal Circuit in *Amgen Inc. v. Hoechst Marion Roussel,* 314 F.3d 1313, 1336 (Fed. Cir. 2003) where the court allowed use of post-filing publications to demonstrate enablement.

Accordingly, Applicants provide herewith a report by Shihabuddin *et al.* (*J Neurosci* 24(47):10642-51, 2004), which supplies evidence that a therapeutic effect may be achieved through implantation of neural progenitor cells in a diseased brain. In particular, Shihabuddin et al. (2004) describes a study in which neural progenitor cells were transplanted into the ASM knockout (ASMKO) mouse. This mouse is a model of Type A Niemann-Pick disease, a disease caused a deficiency in acid sphingomyelinase (ASM), and characterized by an intracellular accumulation of sphingomyelin and cholesterol within the cells' lysosomes. In this study, adult mouse NPCs were genetically modified to express human ASM, suspensions of which were injected unilaterally into multiple regions of the ASMKO mouse brain in the absence of immunosuppression (Shihabuddin et al. (2004) at p. 10643, col. 2., ll. 7-10 and p. 10644, col. 1., ll. 11-22). The results provided "demonstrate that NPCs survive, migrate, and show regionally restricted differentiation in the diseased brain similar to the normal brain" (Shihabuddin et al. (2004) at p. 10643, col. 1, ll. 8-11). Moreover, this report further demonstrates a therapeutic effect. In particular, the report provides that "NPCs retrovirally transduced to express the human ASM protein and implanted into adult ASMKO mouse brain led to a significant reduction in lysosomal storage pathology with reversal of sphingomyelin and cholesterol accumulation" (Shihabuddin et al. (2004) at p. 10643, col. 1, ll. 11-14). The report further provides that the "[r]eversal of pathology, nevertheless, was seen up to 6 weeks after transplantation (the latest time point examined) only in animals receiving transplants of ASM-expressing cells" (Shihabuddin et al. (2004) at p. 10649, col. 2, ll. 37-41).

Finally, the Examiner asserts that "absent any showing that the claimed methods can be used to produce the intended therapeutic effect in an immunocompetent animal, such as a human, rat, mouse, etc., the claimed invention is not enabled by the present disclosure" (Office Action at p. 6). Applicants submit that Shihabuddin et al. (2004) provides evidence that transplanted NPCs can indeed provide a therapeutic effect in a diseased animal. Thus, Applicants submit that the present claims are fully enabled by the present disclosure. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants submit that pending claims 12-17 and 33 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

No fee is deemed necessary with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees required by this submission, or make any credits or overpayments, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER LLP (US)
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO CUSTOMER NUMBER 28213

Attachment: Shihabuddin *et al.* (*J Neurosci* 24(47):10642-51, 2004)